THERAPEUTIC FAILURES IN PULMONARY TUBERCULOSIS*

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UNTIL quite recently the over-all results of the treatment of pulmonary tuberculosis have been very poor. During most of the first half of this century the case fatality rate did not change appreciably and death from progressive disease or continued disability was the expected fate of all but a few tuberculous patients. The discovery of effective antimicrobial drugs and the development of finer thoracic surgical techniques have greatly altered this grim picture.

Carefully controlled studies on large groups of patients have established principles for the use of our presently available therapeutic modalities in the initial treatment of patients with pulmonary tuberculosis which are now almost universally accepted. A few details of what currently constitutes optimum therapy in various groups of patients remain to be worked out. It is generally agreed that patients undergoing initial treatment for tuberculosis should be given a chemotherapeutic regimen that includes isoniazid, and that streptomycin or para-aminosalicylic acid (PAS) or both, should be given concurrently and daily with the isoniazid. This regimen should be continued without interruption for at least a year and often for an even longer period. At an appropriate time during this course of treatment, irreversible and potentially dangerous residual lesions should be identified and if it is feasible, these should be excised.

Numerous exceptions, elaborations, or amendments to this somewhat over-simplified statement of principles may be justified by presently available clinical and laboratory studies. Some investigators would insist that the dose of isoniazid is critical and that either all patients should be tested to identify those individuals who inactivate isoniazid readily or

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that a high dosage of isoniazid should always be employed. The excellent results that have been reported by many clinicians who have used relatively small doses of isoniazid suggest, however, that if a high dosage of isoniazid is important, this is the case in only a very small segment of our patient group. Other observers might suggest that combined therapy is not always necessary and that patients can be selected in whom isoniazid alone is adequate therapy. The place of rest, adrenocortical steroids, triple drug therapy, and daily versus less frequently administered streptomycin could also be introduced. In considering surgical therapy a vigorous debate could be organized as to what constitutes a dangerous or irreversible residue, which residual lesions should be resected, and the place of collapse therapy in a therapeutic program.

In spite of the healthy differences of opinion which this listing indicates, experience shows that the treatment of pulmonary tuberculosis is becoming increasingly standardized and effective. Successful therapy of advanced pulmonary tuberculosis is now so common and so consistently to be expected that it may be fruitful to examine the reasons for failure when this occurs.

Death, continued chronically active disease, relapse, and respiratory insufficiency after the active disease has been controlled, are some of the categories into which therapeutic failures in tuberculosis can be divided.

Death—Vital statistics indicate that the death rate from tuberculosis is declining in nearly all parts of the world where reliable data can be collected. In the last decade a fall in the case fatality rate, which is most often due to improvements in therapy, has also been widely observed. During this same period there has been a steady decrease in the number of patients admitted to tuberculosis hospitals, who died in the hospital. While such data indicate a steady decline in the number of deaths only a review of individual patients dying with tuberculosis can yield qualitative information about such cases.

The case records of one hundred consecutive patients who died on the Chest Service of Bellevue Hospital after the diagnosis of active tuberculosis had been made, have been reviewed. This group includes all such deaths observed on this Service during part of 1954 and all of 1955. Some of the data from these cases are presented in Table I. It can be seen that nearly all of these patients were men, and that the majority were over 50, had not previously had tuberculosis diagnosed or treated

TABLE I—OBSERVATIONS IN 100 PATIENTS DYING WITH ACTIVE PULMONARY TUBERCULOSIS

Male	87
Over 50 years of age	60
Tuberculosis not previously diagnosed	51
No previous chemotherapy for tuberculosis	57
Died in 28 days or less after admission	64
Principal causes of death:	
Non-tuberculous disease	29
Tuberculosis and non-tuberculous disease	28
Tuberculosis	43

and died during the first four weeks after admission.

In 29 of these patients, a review of the record clearly indicated that the principal cause of death was not the co-existing active pulmonary tuberculosis. Among this group were 17 patients with malignant tumors, three with severe vascular disease, four with advanced pulmonary emphysema, four who died of operative or postoperative complications, and one patient with a bleeding peptic ulcer.

In 28 patients it was not possible to unequivocally assign the principal cause of death either to active pulmonary tuberculosis or to the other serious complicating disease which was present. In this group, cases of uncompensated cirrhosis, uncontrolled diabetes, as well as carcinoma, emphysema, surgical accidents and vascular disease were encountered.

In 43 patients far advanced pulmonary tuberculosis clearly seemed to be the principal cause of death. While most patients in this group were debilitated, had evidence of malnutrition, and sometimes dehydration, evidence of other significant organic disease was not detected. Data from this sub-group are presented in Table II. The same characteristics observed in the whole group dying with tuberculosis were observed in this sub-group. It is composed mainly of men over 50 years of age who had not been previously diagnosed or treated. Only seven patients in this group died after the first 28 days in the hospital (30, 31, 32, 66, 110, 111 and 125 days), and three of these deviated from this period by only a few days. While treatment of this group was not standardized or

TABLE II—OBSERVATIONS IN 43 PATIENTS DYING WITH ACTIVE PULMONARY TUBERCULOSIS AS THE ONLY MAJOR CAUSE OF DEATH

Male	38	(88%)
Over 50 years of age	28	(65%)
Tuberculosis not previously diagnosed	31	(72%)
Tuberculosis not previously treated	37	(86%)
Died in 28 days or less after admission	36	(84%)

uniform, all of the generally used supportive measures were available and were employed as indicated. Transfusion, fluid replacement, and support of the blood pressure with sympathomimetic drugs were all commonly employed. Adrenocortical steroids were also used in the treatment of some of these patients. The most frequently employed chemotherapeutic regimen was streptomycin and isoniazid. Some patients were treated with PAS as well. It seemed possible that the presence of drug resistant organisms might have contributed in part to the fatal outcome in five of these 43 patients.

While certain local conditions that influence the selection of patients admitted to and treated at Bellevue Hospital may have affected the character of these observations, it seems probable that our experiences with patients dying of pulmonary tuberculosis are similar to that of many others elsewhere in the United States at this time. Our experiences suggest that in our community death from tuberculosis, *per se*, is unusual. Such deaths occur mostly in older individuals who for some reason avoid medical diagnosis or treatment until they are nearly moribund. Even in this group a fatal outcome can usually be avoided if a supportive regimen can be organized which is adequate to keep the patient alive for the first few weeks. These observations also illustrate again that tuberculosis is coming to be more and more a disease of the older age groups in whom other complicating diseases are to be expected. The very small number of patients in this series who died from tuberculosis after prolonged chemotherapy suggests that even when such therapy does not arrest the disease, it so alters its progressive character that death is an infrequent consequence. This finding may be an important consideration when one must decide whether to use surgical treatment in patients who are poor operative risks, because of ad-

TABLE III—OBSERVATIONS IN 50 CASES RETREATED FOR TUBERCULOSIS

Males		40
Over 50 years of age		11
Extent of Disease:	*Initially*	*At time of retreatment*
Far advanced	18	23
Moderately advanced	10	19
Minimal	5	6
Extrapulmonary tuberculosis only	3	2
Unknown	14	
Reason for terminating initial treatment:		
Irregular medical discharge		26
Discharged from treatment by physician		22
Unknown		2

vanced age, complicating non-tuberculous disease, or respiratory insufficiency.

Continued chronically active disease and relapse. These manifestations of incompletely effective initial treatment are frequently difficult to distinguish and will be considered together here. Patients admitted for the retreatment of pulmonary tuberculosis provide an opportunity to study retrospectively the factors which may contribute to these two categories of treatment failure.

Dr. Julia M. Jones* has reviewed 50 randomly selected patients admitted to the Chest Service, Bellevue Hospital, who required retreatment for tuberculosis. These patients were selected from the same 1954-1955 period as the group of patients in the previous section that died, and no patient that died is included in this group. All had had treatment interrupted for at least one month at the time of admission and most for much longer periods. Because initial treatment had been carried out in many different places and included a variety of different chemotherapeutic regimens, this group is probably representative in many ways of the current problem among patients who require retreatment.

* Jones, Julia M. Retreatment of tuberculosis. Presented at Eastern Section, American Trudeau Society meeting, October 19, 1957, Atlantic City, New Jersey.

Some of the data from this group are presented in Table III. These patients were also found to be predominantly male, but the average age was lower than in the previously considered groups. Far advanced disease predominated, both initially and at the time of retreatment. In the majority (26) of these patients initial treatment had been terminated without medical sanction. In the other 24 patients, it was possible from such information as could be obtained, to identify 11 patients in whom active disease was present when treatment was stopped. In the remaining 13 patients it was frequently difficult to judge whether readmission resulted from a true relapse or from chronically active disease which had never been arrested by initial treatment. Clearly, however, chronically active disease from incomplete initial treatment, rather than relapse, is the principal cause of retreatment in this series. In fact, cases demonstrating true relapse in whom initial treatment was prolonged and uninterrupted, and in whom cavitary residues could not be demonstrated at the conclusion of treatment are so infrequently encountered that it is difficult to define the characteristics of such a group.

A review of patients in this group revealed many stigmata that suggested that severe emotional maladjustments had interfered with initial treatment. Fifteen of these patients were severe alcoholics, seven had histories of major emotional disorders, and 26 had a history of one or more irregular medical discharges. The difficulties attendant on treating such patients are well known to most physicians who work with tuberculous patients. The problem of how to adapt our therapeutic program to meet the needs of this heterogeneous group of disturbed people is probably the most important problem remaining unsolved today in the treatment of tuberculosis in this country. Attempts to make these patients adapt to our presently available treatment regimens have certainly had very limited success.

While it is not the purpose of this presentation to discuss the treatment of this difficult type of patient, in whom treatment has already failed one or more times, it can be said that in this series of patients, reinstituted therapy usually resulted in the disease again being brought under control. Chemotherapy, often with the less commonly used antibiotics, and resectional pulmonary surgery, seemed to completely control the pulmonary tuberculosis in many of these individuals, and in others to control it sufficiently for them to resume their program of irregular medical discharges.

Respiratory insufficiency after completed treatment. While this type of therapeutic failure has not been studied in a systematic fashion, scattered observations on individual cases indicate that while far advanced disease must have been present in all such cases, other factors may also be important in causing disabling respiratory insufficiency. Patients have been observed with very far advanced pulmonary tuberculosis who after the disease has been completely arrested have only minor changes in lung volumes and ventilatory function. At the same time other patients have been observed who are left with complete disability and all the clinical and physiologic findings of advanced pulmonary emphysema. In this latter group there is often either a history of multiple very fine, widespread bronchogenic disseminations of the type seen with tuberculous laryngitis or repeated untreated hemoptyses, or suggestive evidence that pulmonary emphysema unrelated to the tuberculosis has developed simultaneously.

In conclusion, our experience indicates that most therapeutic failures in pulmonary tuberculosis can usually be attributed to one of the following: far advanced disease at the time of initial discovery; inability of the patient for social or psychological reasons to accept a complete course of treatment; failure of the physician to administer adequate chemotherapy or to see the need for adjunctive surgery; and the presence of other complicating diseases.